In the name of God

Title:

Cancer systems biology

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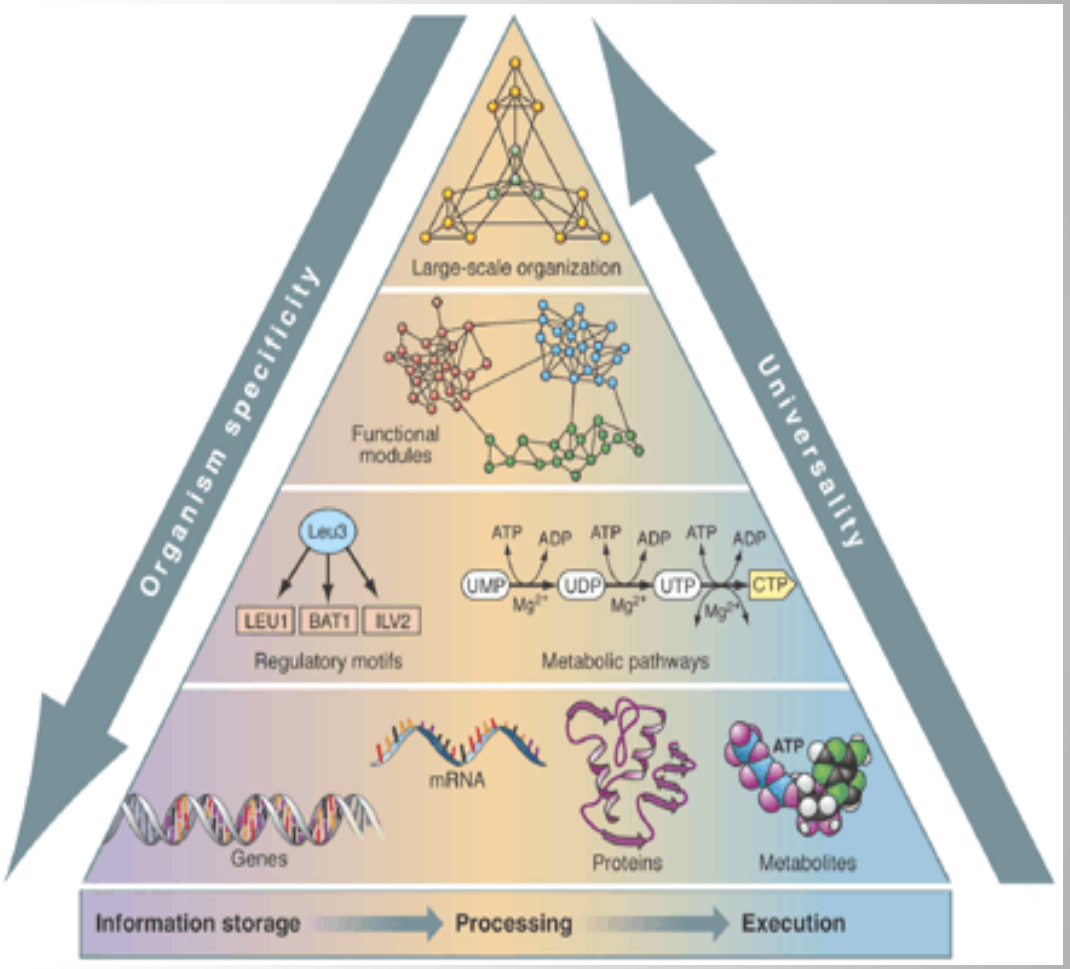
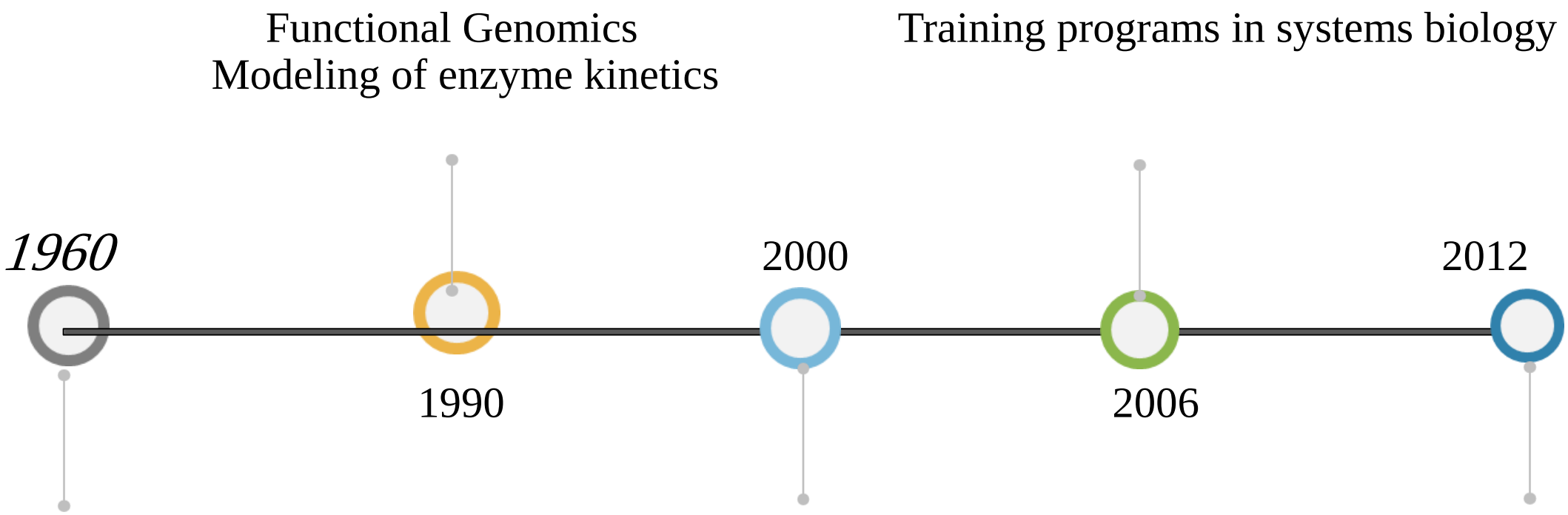
Contents:

What is systems biology?

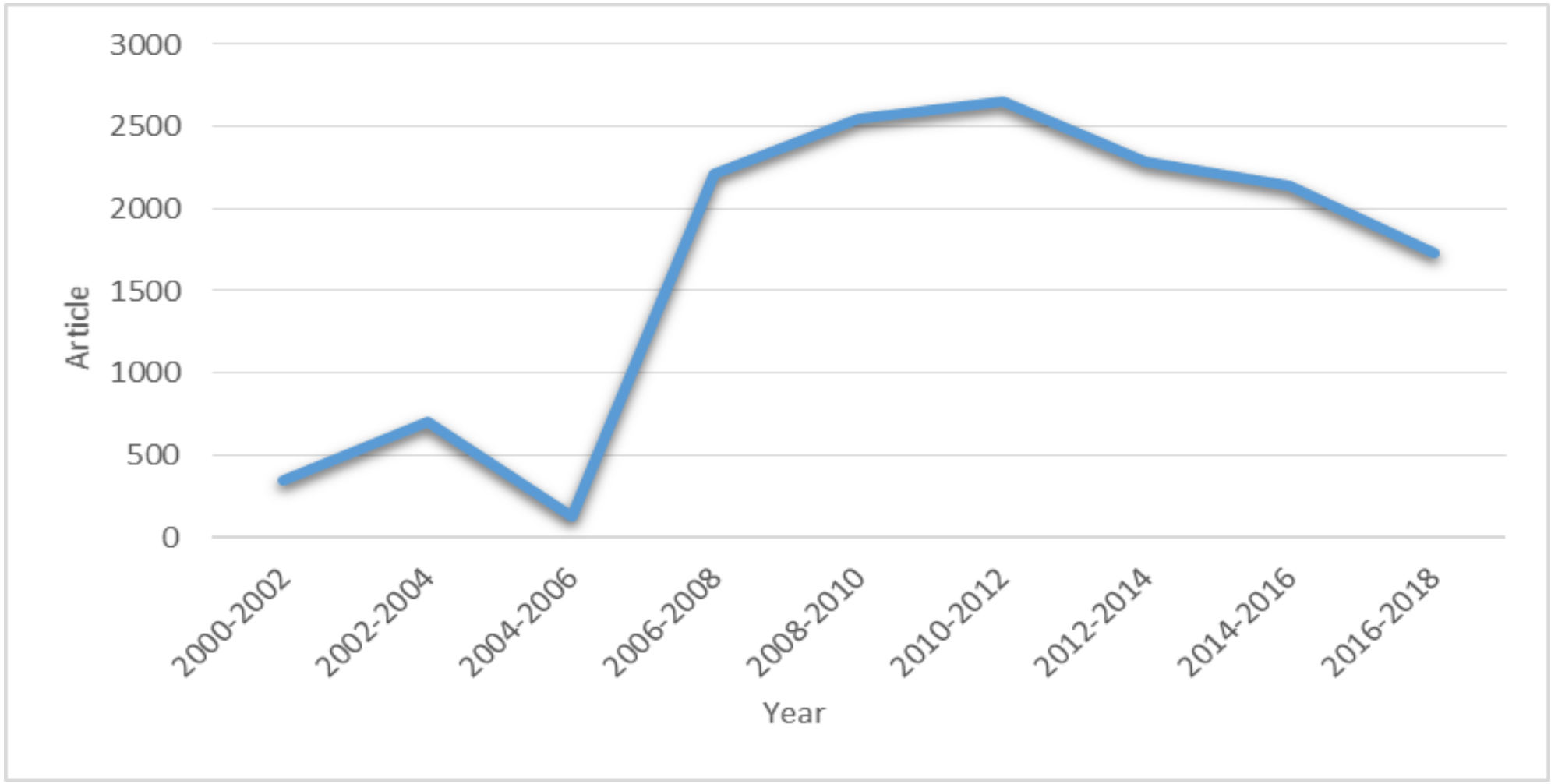
- *The computational and mathematical modeling of complex biological systems*
- *A biology-based interdisciplinary field that focuses on complex interactions within biological systems*
- *Using a holistic approach to biological research(1)*



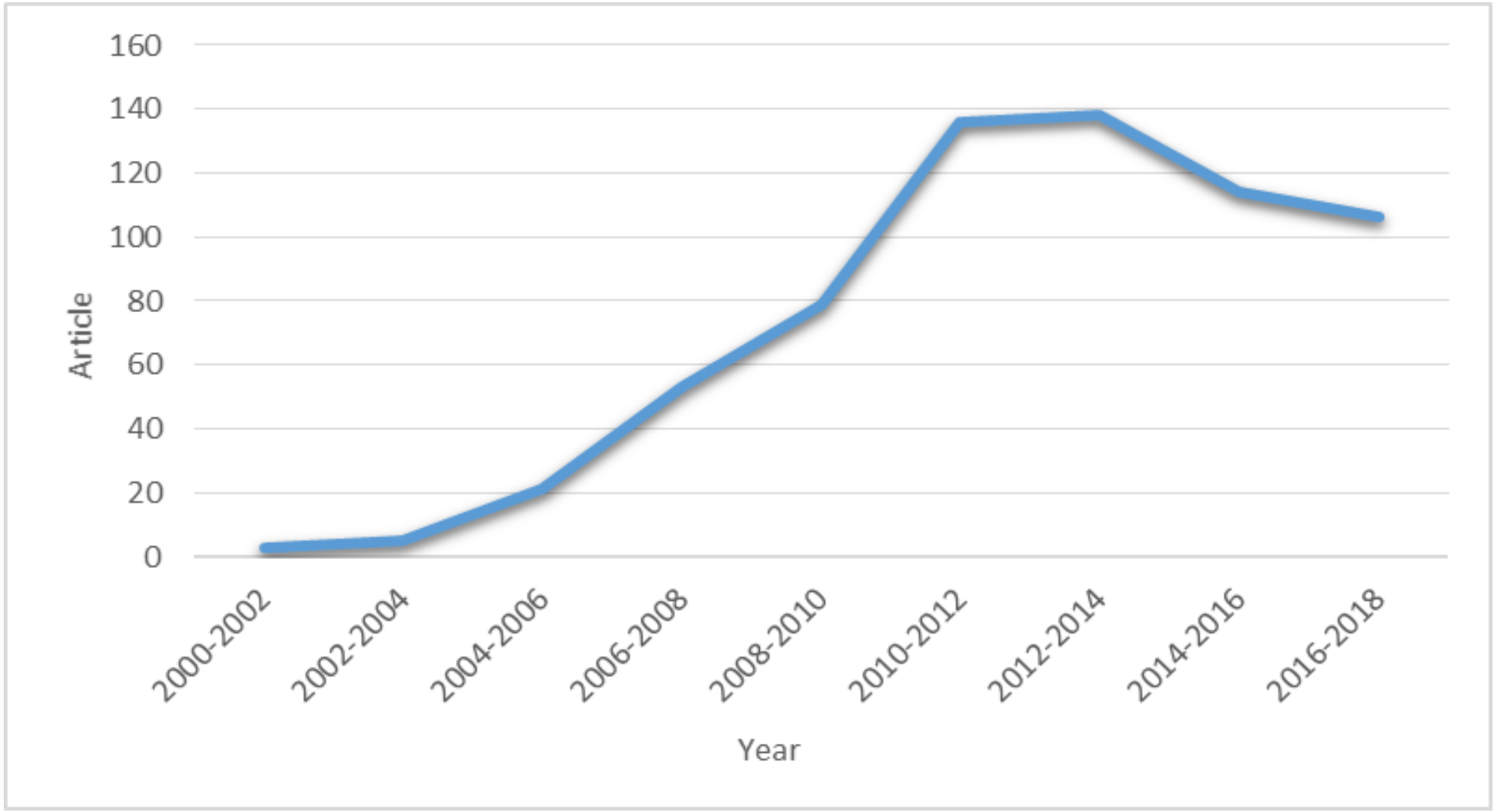
Systems biology timeline



Systems biology Chart
(Google scholar)



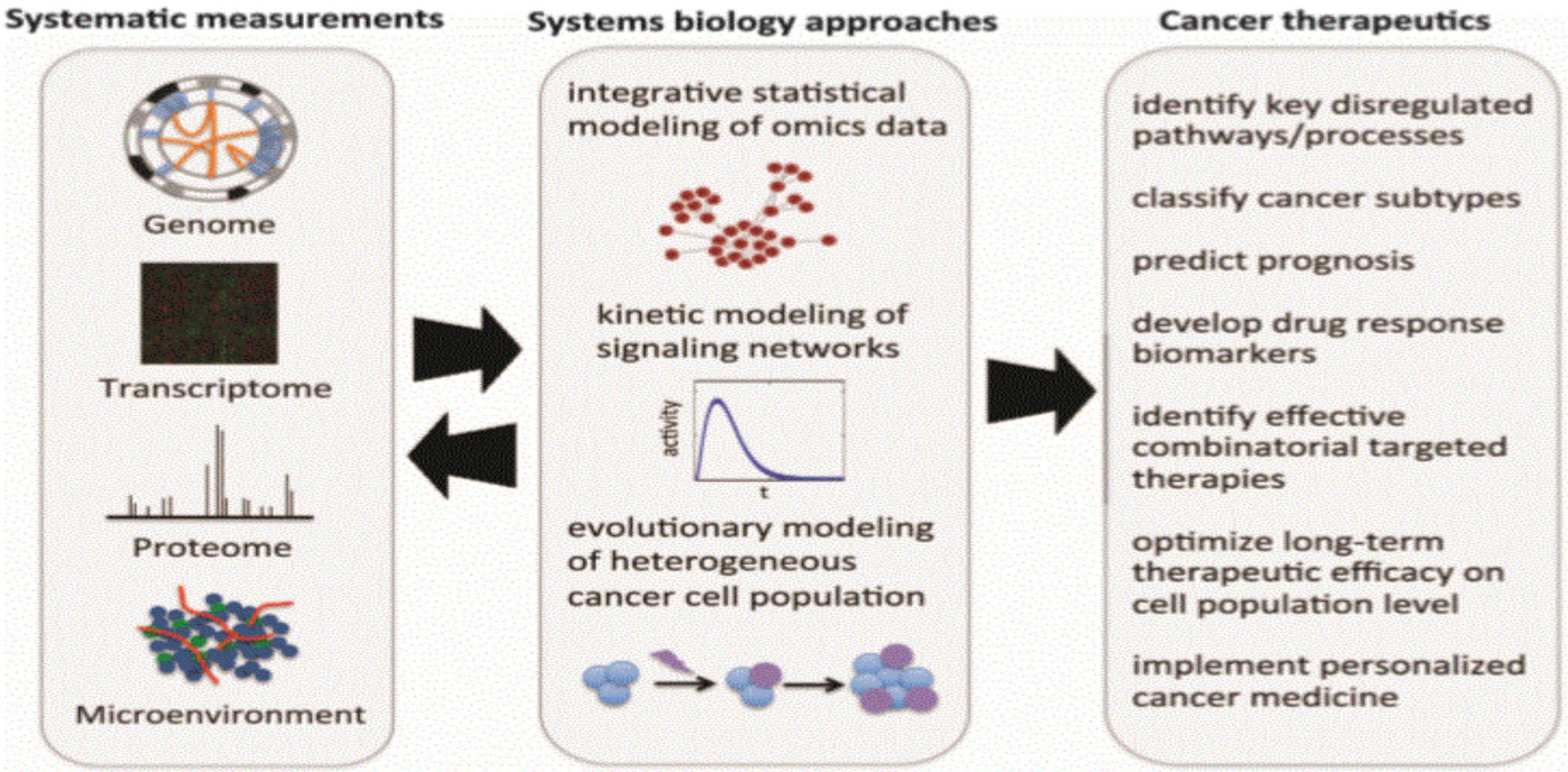
Cancer systems biology Chart
(Google scholar)



Cancer systems biology:

- *Developing an increasingly holistic view of cancer development and progression*
- *Understanding how complex cancer-associated deregulations shape malignant states and phenotypes(2)*
- *Understanding cancer initiation and progression*
- *Discovery and implementation of more effective anticancer therapeutic strategies(3)*

A summary of cancer systems biology approaches to guide cancer therapy(2)



Cancer

- *Caused by corruption of normal biological circuits and processes to sustain uncontrolled proliferative growth*
- *Characterized by a complex spectrum of alterations that affect multiple scales ranging from molecular activity within cells onto communication between cells and tissues(4)*

Why cancer systems biology?

1. Highly complex patterns of interactions leads to great challenges in understanding cancer progression and designing effective cancer therapy

2. At the genomic level, frequent disruption of the DNA complicating the discovery of underlying drivers of tumor progression(2)

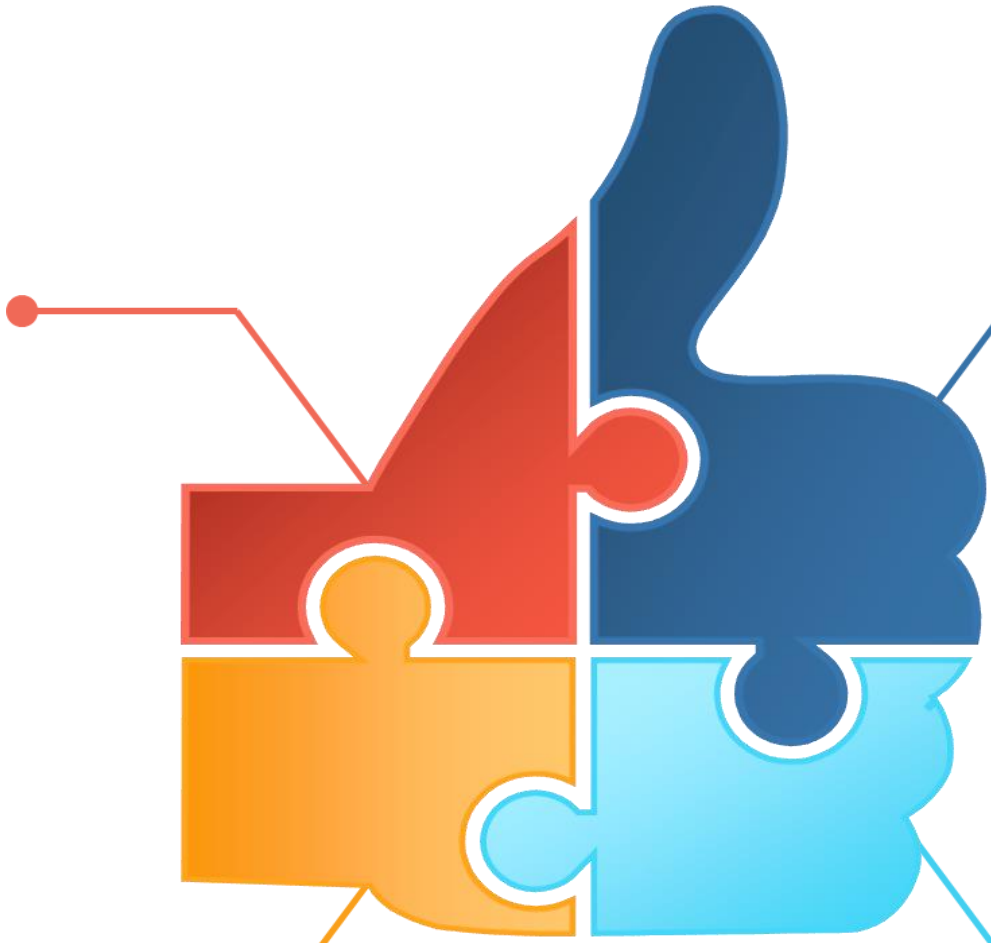
3. At the protein level, complex signaling networks makes it difficult to anticipate the influences of oncogenic perturbations and reverse those influences with pharmacological agents

4. At the tissue level, interactions between a tumor and its local environment influence tumor growth and invasion(2)

5. in many cancer types, substantial heterogeneity of molecular alterations in patient population yields highly variable clinical responses to the same treatment(2)

- *systems biology approaches that can manage and model this complexity will be needed to identify and validate targets, biomarkers and discover more effective and less toxic therapeutic strategies(5)*

PROBING CANCER COMPLEXITY



Genomic level

Tissue level

Protein & posttransnational level

Personalized cancer medicine

PROBING CANCER COMPLEXITY AT THE GENOMIC LEVEL

Cancer is a disease driven by the accumulation of genomic and epigenomic alterations

- *Genomic alterations:*
  - *1.point mutations*
  - *2.translocations*
  - *3. copy number variations*
- *Epigenomic alterations:*
  - *1.hyper- or hypomethylation of specific regions and genes*
  - *2. changes in levels of histone modifications(2)*

genetic and epigenetic alterations:

1) drivers:

confer selective growth advantage and are thus causal for malignant transformation and tumor progression.

2) passengers:

accumulate in the course of cell divisions and contribute little to malignant phenotypes.

- *Systems-level analyses have made creative use of passenger mutations to uncover potential therapeutic strategies(2)*

Complexity of the cancer genome:

- *The rate of genomic alteration occurrence plays a central role in this evolutionary process(6)*
- *In cancer cells, oncogene-induced DNA replication stress and/or direct disruptions of DNA repair genes leading to widespread genomic instability*
- *Cancer cells display extensive intratumoral and intertumoral heterogeneity(2)*

- *Intratumor heterogeneity can further seed intertumoral heterogeneity among different metastases, if :*

different metastases arise from distinct founder cells that have escaped from the primary tumor(3)

- *Darwinian point of view:*

therapeutic intervention can act as an imposed selective pressure that potently and rapidly alters subclonal constitution(2)

Interrogating the cancer genome using next-generation sequencing:

- *Next-generation sequencing : ultrafast, high-throughput and affordable sequencing via massively parallel assessment of sequence fragments(7)*
- *Whole-genome sequencing of tumor samples with paired normal tissue is now routinely used(2)*

- *Whole-exome sequencing :*

1) more cost-effective and higher coverage alternative to whole-genome sequencing

2) detects aberrations that directly alter protein functions with high sensitivity(6)

- *RNA sequencing : detect gene expression changes in tumors, revealed novel expressed variants, gene fusions and splicing alterations in cancers*
- *single-cell sequencing: valuable information on tumor heterogeneity and clonal evolution history can be extracted(8)*

Systems approaches for addressing cancer genome complexity:

- *Even though specific genomic alterations vary from patient to patient, they usually result in disruption of a few key pathways and processes*
- *Systems-level analysis has provided insights into common mechanisms underlying cancer pathogenesis(2)*

PROBING CANCER COMPLEXITY AT THE PROTEIN AND POSTTRANSLATIONAL LEVELS:

- *In normal tissues, the homeostasis of signaling networks is precisely maintained*
- *In cancer cells, genomic and epigenetic alterations leading to aberrant protein expression or function disrupt this homeostasis(9)*
- *Loss of negative regulator expression in signaling networks can remove important brakes on signaling, resulting in uncontrolled response(6)*

Experimental probing of aberrant function in signaling networks:

- *large-scale protein profiling is increasingly used to directly and systematically monitor signaling pathway activities in cancer cells*
- *mass spectrometry-based phosphoproteomics: identifies phosphorylated proteins(2)*

Modeling the dynamics of signaling networks:

- *Kinetic modeling of protein–protein interactions:*
- *reproduce signaling dynamics in silico and make quantitative predictions of the effect of various network alterations*
- *These models demonstrated great potential in identifying drug response biomarkers, resistance mechanisms, and synergistic drug combinations(10)*

Data-driven systems biology analysis for dissecting aberrant signaling function:

- *The analysis of proteome-wide profiles has provided important insights into cancer signaling networks and into how to target their aberrant functions(5)*

PROBING CANCER COMPLEXITY AT THE TISSUE LEVEL:

- *Tumor microenvironment (TME): plays an active role in tumor progression*

- *Cancer cells benefit from the microenvironment by acquiring nutrients and various biochemical factors(2)*

- *targeting the TME may yield efficient and perhaps less toxic anticancer therapy*
- *The plasticity of tumor microenvironment have led to emergence of drug resistance in various TME-targeted therapies(3)*

Experimental approaches for analyzing the tumor microenvironment:

- *mRNA and protein arrays on microdissected tumor biopsy samples or xenografted tumor lesions:*

  identified key factors and pathways, TME-related molecular signatures predictive of clinical outcome

- *cross-species hybridization of microarrays:*

  simultaneous assessment of gene expression in both tumor and host cells via separate hybridization(2)

❖ *In vivo imaging:*

examine tumor–stroma morphology and interactions or assay specific molecular markers such as pH, hypoxia or proteases with fluorescence probes(4)

❖ *In vitro culture models of tumor cells with key components of the microenvironment:*

discover important interactions between stroma and tumor cells

❖ *Modeling the TME:*

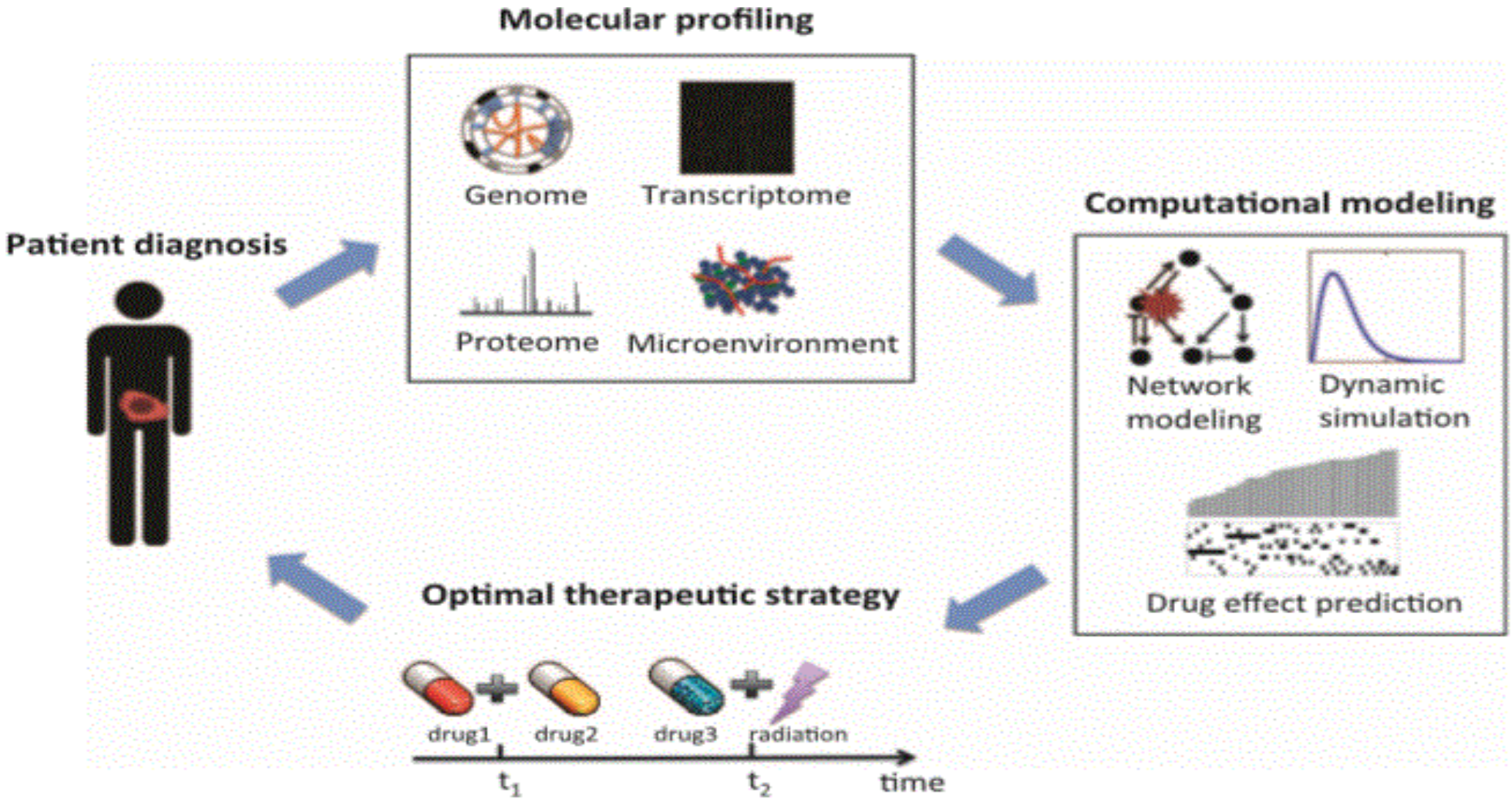
provided important insights into how tumor and the microenvironment coevolve(2)

CANCER SYSTEMS BIOLOGY AND PERSONALIZED CANCER MEDICINE:

- *computational platform for identifying clinically relevant alterations based on whole-exome sequencing data from formalin-fixed, paraffin-embedded tumor samples:*

Applying this method to patients of various tumor types successfully identified potential clinical targets in 15 out of 16 patients(2)

model-based strategy for personalized cancer medicine(2):



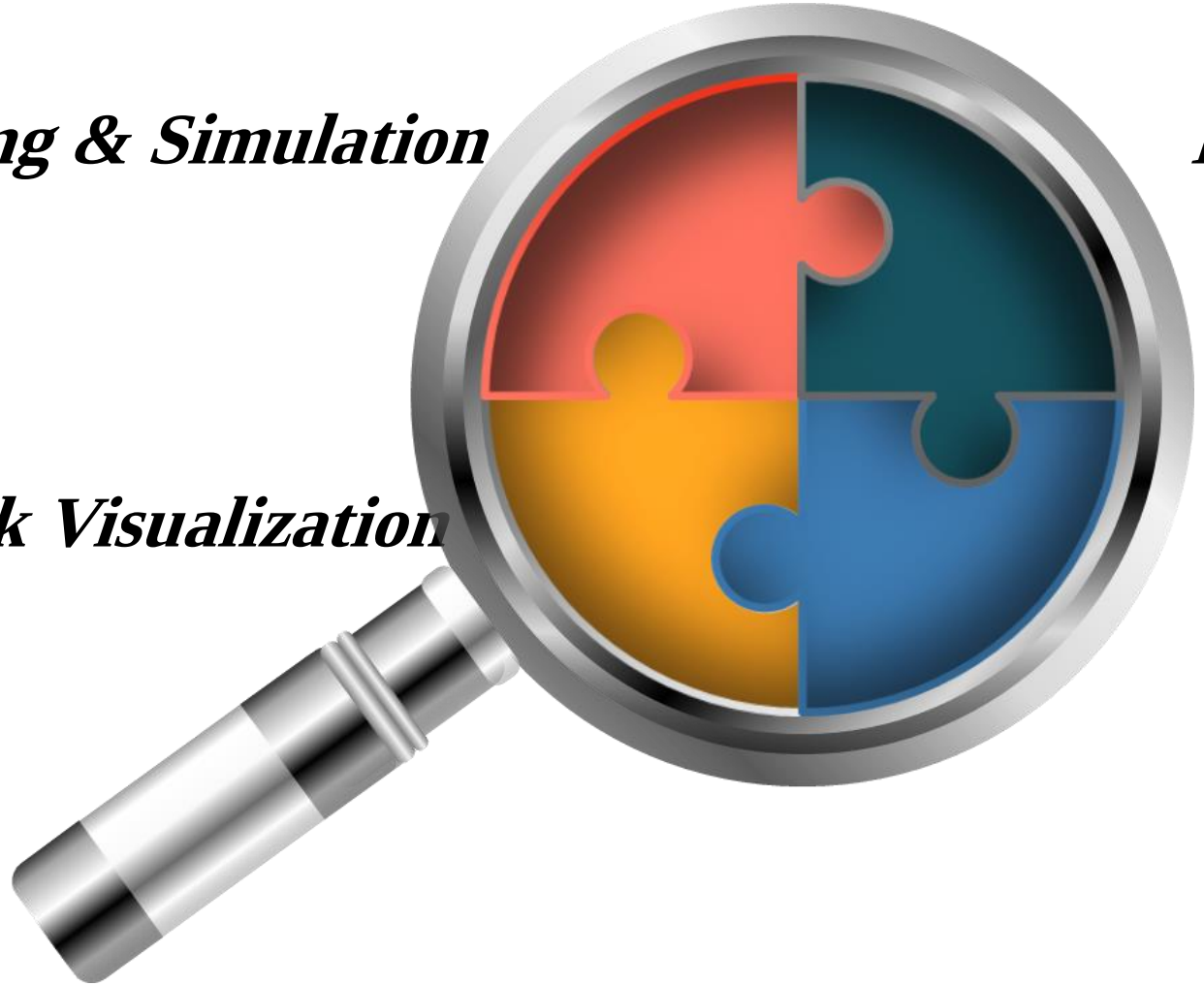
CONCLUSION:

- *Cancer is an extremely complex disease featuring systems-level disruptions(3)*
- *Cancer systems biology operates on large multiscale data set to develop integrative and predictive models*
- *The integrative and dynamic nature of these models makes them extremely powerful in addressing some of the major challenges in cancer biology*
- *As cancer treatment approaches a more personalized era, cancer systems biology will play a central role in the development of integrative model-based cancer medicine(2)*

Systems biology databases & tools

Modeling & Simulation

Pathway



Network Visualization

Protein-pro interactio

Modeling & Simulation tools:

- ***CellDesigner*** ***(http://www.celldesigner.org/)***
- ***Jarnac/JDesigner*** ***(http://sbw.kgi.edu/)***
- ***COPASI*** ***(http://www.copasi.org/)***
- ***E-cell*** ***(http://www.e-cell.org/)***

Network Visualization Tools:

- ***Cytoscape*** ***(http://www.cytoscape.org/)***
- ***BioTapestry*** ***(http://www.biotapestry.org/)***
- ***BioUML*** ***(http://www.biouml.org/)***
- ***CADLIVE*** ***(http://www.cadlive.jp/)***
- ***Edinburgh Pathway Editor***
  (http://www.bioinformatics.ed.ac.uk/epe/)

Pathway database:

- ***KEGG(Kyoto Encyclopedia of Genes and Genomes) (http://www.genome.jp/keg/)***
- ***REACTOME (http://www.reactome.org/)***
- ***MetaCyc (http://www.metacyc.org/)***
- ***EcoCyc (http://www.ecocyc.org/)***

Protein-protein interaction database:

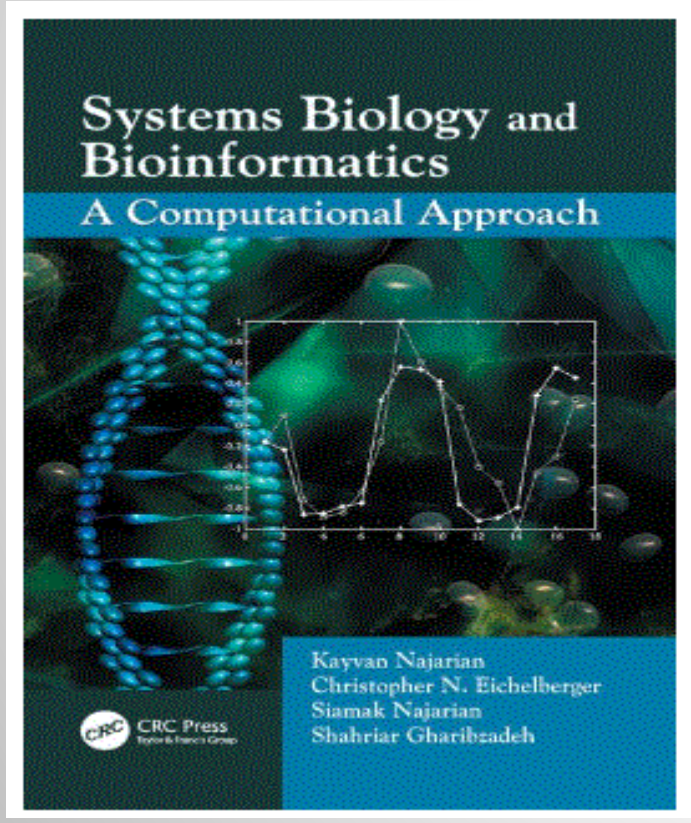
- ***BINDplus (Biomolecular Object Network Database) (http://www.thomsonreuters.com/products_service/scientific/BINDplus)***
- ***DIP (The Database of Intracting Proteins) (http://www.dip.doe-mbi.ucla.edu/dip/Main.cgi)***
- ***MINT (The Molecular INTeraction database) (http://www.mint.bio.uniroma2.it/mint/Welcome.do)***
- ***STRING(Search Tool for the Retrieval of Intracting Genes/Proteins) (http://www.string.embl.de/)***

Books

Systems biology & Bioinformatics

Published date: May 31,2017

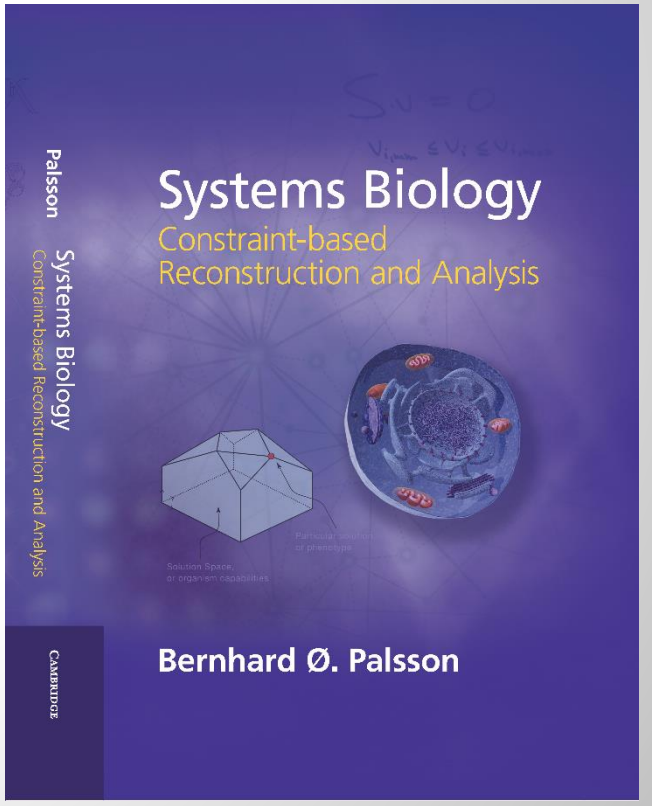
140 pages



Systems biology

Published date: January 2015

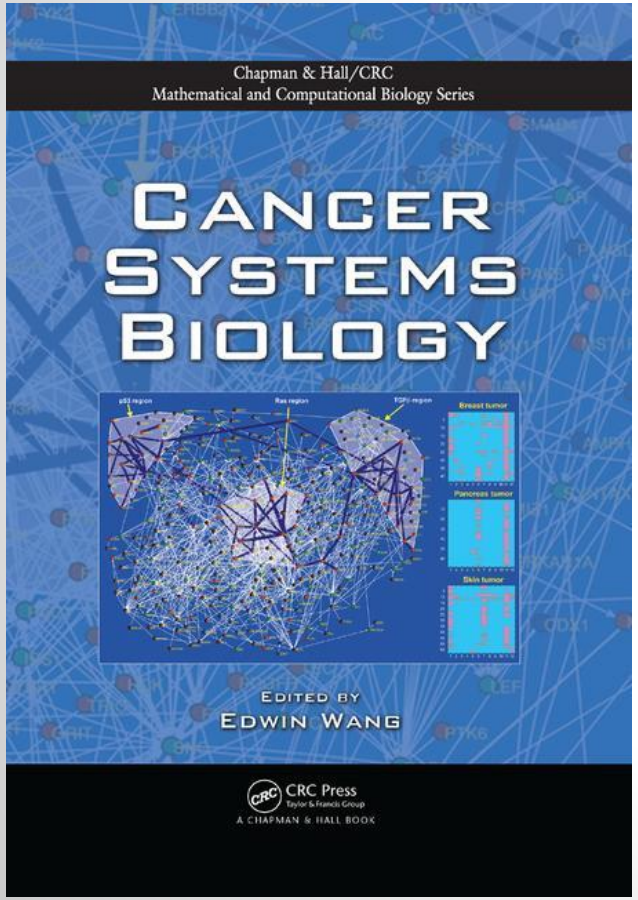
University of California



Cancer systems biology

Published date: June 14,2017

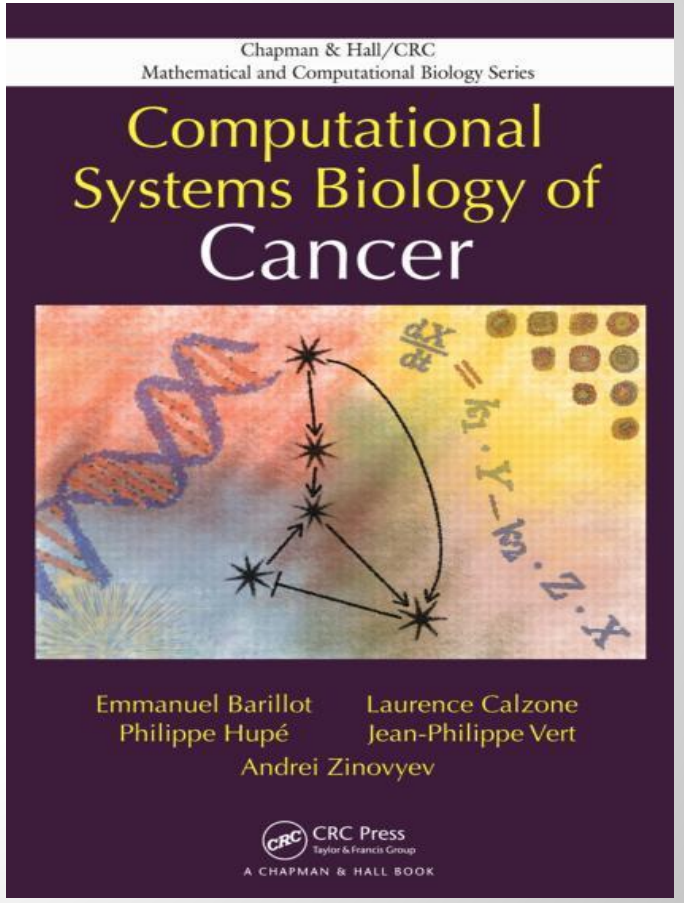
456 pages



Computational systems biology of cancer

Published date: August 25,2012

461 pages



References:

1) Rexxi D. Prasasya[1], Dan Tian[1], Pamela K. Kreeger. Analysis of cancer signaling networks by systems biology to develop therapies

2) W Du and O Elemento. Cancer systems biology: embracing complexity to develop better anticancer therapeutic strategies

3) Evangelia Koutsogiannouli1, Athanasios G. Papavassiliou2 & Nikolaos A. Papanikolaou. Complexity in cancer biology: is systems biology the answer

4) Hiroaki Kitano. Systems Biology: A Brief Overview

5) Ali Masoudi-Nejad, Yazdan Asgari. Metabolic Cancer Biology: Structural-based analysis of cancer as a metabolic disease, new sights and opportunities for disease treatment*

6) David Henderson1,, Lesley A. Ogilvie2,3, Nicholas Hoyle4, Ulrich Keilholz5, Bodo Lange3, Hans Lehrach2,3,6,** , on behalf of the OncoTrack Consortium. Personalized medicine approaches for colon cancer driven by genomics and systems biology: OncoTrack*

7) Fabian V. Filipp. Precision medicine driven by cancer systems biology

8) Jens Nielsen. Systems Biology of Metabolism: A Driver for Developing Personalized and Precision Medicine

9) Dana Faratian,1 Alexey Goltsov,2 Galina Lebedeva,2 Anatoly Sorokin,2 Stuart Moodie,2 Peter Mullen,1 Charlene Kay,1 In Hwa Um,1 Simon Langdon,1 Igor Goryanin,2,3 and David J. Harrison. Systems Biology Reveals New Strategies for Personalizing Cancer Medicine and Confirms the Role of PTEN in Resistance to Trastuzumab

10)Annesofie Lærke Hansen, Rebecca M Lennen,Nikolaus Sonnenschein and Markus J Herrga˚ rd. Systems biology solutions for biochemical production challenges


Thank
you!!